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PHYSICIAN PRESCRIBING PRACTICES AND ADVERSE DRUG REACTIONS: A Proposal for Further FDA Regulation of Prescription Drugs

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I. Introduction.

In 1938 the Food and Drug Administration (FDA) adopted regulations which created a category of prescription drugs to be distributed only by order of a physician or other licensed medical personnel. This categorization, along with the extensive regulation of the approval, labelling and marketing of human drugs, has substantially reduced the risks which accompanied self-medication. However, the current regulatory regime does not place any limits on physician prescribing. This shortfall in regulation fails to protect patients from poor prescribing practices and exposes these patients to otherwise preventable adverse drug reactions (ADRs). Attempts to remedy this shortfall have been unsuccessful. Under the existing Food, Drug and Cosmetic Act¹ (FD&C Act) and its judicial interpretation in *American Pharmaceutical Ass'n v. Weinberge*², the FDA seemingly does not have the authority to regulate physician prescribing practices.

This paper will examine the problem of adverse drug reactions in the context of the current regulatory regime for prescription drugs. Section II will describe the current regime, and Section III will examine its shortfalls in dealing with adverse drug reactions. Section IV will suggest features which should be added to the current regime which would protect patients from careless prescribing practices, and Section V will examine the FDA's legal authority to make such changes.

II. The Current Regulatory Regime.

The prescription drug category was created by the FDA through regulations promulgated in 1938. These regulations were aimed at protecting those unskilled in the uses of drugs and relied upon the manufacturer to decide which drugs would be given prescription status such that consumers could not purchase the drug without first consulting a physician.³ The FDA enforced the regulation by suing drug companies for mislabeling when it disagreed with their categorizations.⁴

¹21 U.S.C. 321 *et seq.*

²377 F.Supp. 824 (D. D.C. 1974), *affd per curiam*, 530 F.2d 1054 (D.C. Cir. 1976).

³Peter Temin, *The Origins of Compulsory Drug Prescriptions*, 22 J.L. & EcON. 91(1979).

⁴Id.

Congress clarified the legal status of prescription drugs in the 1951 Durham-Humphrey amendment to the FD&C Act.⁵ Instead of leaving the categorization of a particular drug to the discretion of the manufacturer, which lead to a lack of conformity and confusion when the same drug was given a different status by different manufacturers, the amendment set guidelines for drawing the line between over-the-counter and prescription drugs.⁶

The Durham-Humphrey amendment, which can be found in section 502(b) of the FD&C Act, lists factors that are considered when making the decision to confer prescription status on a drug. These factors are (1) the drug's toxicity or other potentiality for harmful effect, (2) its method of use, and (3) its lack of safety except under the supervision of a practitioner licensed by law to administer the drug.⁷ Accordingly, prescription drug status is

iven to habit forming drugs listed in section 502(d) and to new drugs as a condition of their approval.⁸ Drugs with these characteristics are dispensed only by order of a licensed practitioner.⁹ Prescription drugs must be labelled in a way such that the prescribing physician, and not necessarily the consuming patient, is made aware of its proper usage and apparent risks.¹⁰

All new drugs, whether prescription or over-the-counter, are tested and reviewed before approved for human use. After pre-clinical testing, the FDA must approve a claimed exemption for an investigational new drug (IND) before research on use of the drug in human beings can begin. If the IN) is not rejected, the manufacturer will test the drug in three phases. During phase I, the drug is tested on one or two subjects (usually healthy) to determine drug metabolism, excretion and, most importantly, safety. If there are no apparent adverse effects which would limit the drug's use in humans, testing moves into phase II where the drug is administered to a small number of patients with the disease the drug is aimed to treat. If the drug, which has been deemed safe in phase I, also is shown to be effective in phase II, the drug then will be tested on hundreds of patients in controlled clinical trials in phase III.¹¹

The results of clinical testing from all three phases are included in a New Drug Application (NDA) which is then reviewed by the FDA and either approved or disapproved. FDA approval will be granted only if the drug is safe and effective, can be manufactured consistently, has benefits which when used properly outweigh its risks, and is accompanied by adequate labelling of proper use and risk warnings.¹² Once the drug is approved, physicians may prescribe

⁵Durham-I-umphrey Amendment, 65 Stat. 648 (1951).

⁶Temin, *supra* note 3.

⁷FD&C Act, §502(b)(1)(B).

⁸Id., §503(b)(1)(A)&(C).

⁹Id., §503(b)(1)(C).

¹⁰Id., §502(f); *see also* Magee v. Wyeth Laboratories, Inc., 214 Cal.App.2d 340, 29 Cal. Rptr. 322 (1963) (prescription drug manufacturer responsible only for getting adequate warning to physician, not for ensuring warning is translated to patient).

¹¹SUBCOMM. ON SCIENCE, RESEARCH & TECHNOLOGY OF HOUSE COMM. ON SCIENCE & TECHNOLOGY, THE FOOD AND DRUG ADMINISTRATION'S PROCESS FOR APPROVING NEW DRUGS, 96th Cong., 2d Sess. (1980), *reprinted in* Hurr & MERRILL, FOOD AND DRUG LAW, 514-516 (2d ed. 1991).

¹²Id. at 520.; FD&C Act, §505(d).

the drug without limitation at their own discretion.

.The Problem of Adverse Drug Reactions.

Although clinical studies of new drugs are extensive - lasting several years, involving hundreds of patients and costing millions of dollars - they do not guarantee that the drugs are safe or that all side-effects have been discovered. The limited number of and types of patients selected during these trials may be insufficient to predict the occurrence of adverse drug reactions (ADRs) in the general population or in specific subgroups (such as the elderly).¹³ In addition, ADRs may be revealed by the use of the drug in less controlled settings by physicians with less skill, less training and less opportunity to adhere to the suggestions in the labelling of the drug.¹⁴

Congressional investigators estimated that more than half of the new drugs sold in the United States will cause severe or fatal ADRs after they are approved by the FDA.¹⁵ Serious

side-effects were defined in their study as any ADR which could lead to hospitalization, increased length of hospital stay, severe or permanent disability, or death.¹⁶ Heart failure, shock, convulsions, kidney failure, blood disorders, birth defects, fetal toxicity and blindness were among the observed ADRs.¹⁷ These ADRs have astounding health and financial consequences. In 1969 it was estimated that one seventh of all hospital stays is devoted to the care of drug toxicity running up an annual bill of \$3,000,000,000.¹⁸ Presently, it is estimated that up to 2 million patients are hospitalized each year and as many as 140,000 people die from ADRs.¹⁹

Under section 505(k), the FDA has the authority to require drug manufacturers holding an NDA to maintain records and make reports. The FDA has used this authority to promulgate regulations which require prompt reporting of serious adverse reactions.²⁰ Upon a finding that an approved drug has serious side-effects, the FDA has the authority under section 505(e) of the FD&C Act either to withdraw the drug or to require additional warnings of the danger to be placed on the label. Being the only options which the FDA can exercise, the treatment of drugs with known adverse reactions essentially is all-or-nothing: the drug is either completely removed from the market or it remains on the market for physicians to freely

rescribe. In many situations neither will be an efficient choice.

¹³Peter H. Rein stein, *Reporting of Adverse Drug Events: A Key to Postmarketing Drug Safety*, 46 AM. FAM. PHYSICIAN 873 (1992).

¹⁴*Drug Safety: Hearings Before a Subcomm. of the House Comm. on Govt. Operations*, 88th Cong., 2d Sess.(1964)(statement of George Larrick, FDA Commissioner) reprinted in Hurr & MERRILL, *FOOD AND DRUG LAW*, 522-524 (2d ed. 1991).

¹⁵*FDA Drug Review Post Approval Risks 1976-85* (GAO/PEMD-90-15).

¹⁶Donald C. Dilworth, *Half of FDA-Approved Drugs Show Harmful Side-Effects*, TRIAL, August 1990 at 14,15.

¹⁷Id.

¹⁸Kenneth L. Melmon, *Preventable Drug Reactions - Causes and Cures*, 284 N. ENG. J. MED. 1361 (1971).

¹⁹Doug Podolsky and Penny Loeb, *Dangerous Drugs*, U.S. NEWS & WORLD REPORT, January 9, 1995 at 49,50.

²⁰21 C.F.R. §314.80.

The first will deprive desperate patients of highly effective, albeit risky, drug treatments. The second will expose the drug taking public to risks limited only by physician discretion.

The approval and withdrawal process for prescription drugs assumes that the drugs will be used properly.²¹ The current regime fails to provide for the situation in which ADRs arise from physician misuse, even though poor prescribing practices has been identified as a major cause of ADRs.²² Physicians are prescribing too many pills without setting a therapeutic end point inadvertently causing their patients to reach a toxic end point instead.²³ They are using excessive numbers of medications in vulnerable populations²⁴ and are prescribing drugs using information provided by the manufacturer's sales force, rather than that contained in the FDA approved package inserts.²⁵

The prescription drug category was created so that patients would benefit from the advice of their physicians when dealing with certain higher risk drugs. However, the current regulatory framework inadequately deals with the recognized problems of poor prescribing practices. Under this system the drug consuming public is needlessly exposed to avoidable ADRs and subsequently risks losing access to highly effective drugs.

v. Expanded Regulatory Regime: Restricted Drug Status

Recognizing that doctors are not always making informed decisions when determining how to medicate, a regulatory system must be established to standardize physician prescribing practices. A middle ground should be added to the current all-or-nothing regulatory regime which would allow the FDA to place restrictions on the use of drugs with harmful ADRs. Such a system should eliminate the guesswork in prescribing, thus providing for a reduction in ADRs without requiring the FDA to remove the drugs in question from the marketplace.²⁶

Instead of banning drugs outright or allowing physicians to prescribe drugs freely, the FDA should promulgate regulations placing drugs with a high risk of ADRs in a restricted category and allowing physicians to prescribe restricted drugs only upon meeting specified conditions. Such conditions would include mandatory laboratory tests which monitor for signs of known ADRs, and limitations on the number of refills allowed on a given prescription to ensure periodic re-evaluation of the patient's condition. Pharmacists would not be allowed to dispense the restricted drug unless the results of the specified laboratory tests were indicated on the prescription. In the case of exceptionally

²¹FD&C Act §505(d) requires the FDA to withhold approval if test results show that the drug is not safe under conditions prescribed, recommended or suggested in proposed labelling, and §505(e) gives the FDA the power to revoke approval if proven unsafe under these same conditions.

²²Melmon *supra* note 18.

²³*Id.*

²⁴Stephen B. Soumerai, *Special Communication: Principles of Educational Outreach ('Academic Detailing') to Improve Clinical Decision Making*, 263 JAMA 549 (1990).

²⁵Podolsky & Loeb, *supra* note 19 at 51.

²⁶Hershel Jick, *Adverse Drug Reactions: The Magnitude of the Problem*, 74 J. **ALLERGY CLIN. IMMUNOL.** 555 (1984) (Recognizing that many ADRs are preventable).

toxic drugs, an additional safeguard could be added which required the physician's explicit approval of the drug therapy when test results fall below a stated healthy threshold.

The FDA would have the discretion confer restricted status upon a drug. Drugs which should be given immediate attention by the FDA are new drugs, drugs with known serious side-effects, and drugs distributed to at-risk populations.

Ideally, all new drugs would be given restricted status. The drug would remain in this status for three years, the time in which serious risks are usually identified.²⁷ Such classification would enable the FDA and the manufacturer to better monitor for adverse effects otherwise missed in clinical trials. Currently, the reporting of adverse effects is voluntary and it was estimated that only 1 percent of all serious drug reactions are reported to the FDA.²⁸ By requiring laboratory tests for evidence of toxicity from all new drugs, the regulations would provide both the physician and pharmacist with more than anecdotal evidence on which to base their reports thereby encouraging reporting. Such tests also would result in increased patient awareness, prompting the patients to report any unusual reactions to their pharmacist or physician. An obvious problem with restricting all new drugs is that the ADRs of these drugs, if any, are not yet known. Running a battery of arbitrarily chosen laboratory tests would waste health care resources: being time-consuming, expensive and possibly unrevealing.

The FDA should categorize as restricted any drug which has a narrow benefit to risk ratio, i.e. drugs which are highly effective, yet have serious ADRs. In this case the ADR will have been identified, and the FDA would require monitoring for this ADR when the drug is prescribed rather than completely withdrawing the drug from the market. An example of a drug for which this treatment would be appropriate is the anti-epilepsy drug Felbatol. Since its approval, ten people taking the drug have developed acute liver failure and twenty-one people have developed aplastic anemia (a sometimes fatal bone marrow disease). Of these people, seven have died. The drug's manufacturer, Carter-Wallace, Inc., has issued warnings to doctors of these ADRs, recommending weekly liver function tests during Felbatol treatment and the use of this drug only in patients who have not responded to other treatments. Under the current regulatory system these warnings may fall on deaf ears, allowing the number of fatal reactions to increase and prompting the FDA to withdraw its approval. However, under the proposed system these warnings would be implemented through regulation: reducing the risk of liver failure while retaining the availability to the 10,000 to 12,000 patients for whom this treatment is their last resort.²⁹

Acute liver failure caused by Felbatol was observed across patient

²⁷Donald C. Dilworth, *Half of FDA-Approved Drugs Show Harm fill Side Effects*, **TRIAL**, August 1990 at 14.

²⁸Doug Podolsky & Penny Loeb, *Dangerous Drugs*, U.S. **NEWS & WORLD REPORT**, January 9, 1995 at 51.

²⁹*Felbatol May Cause Acute Liver Failure*, FDA **CONSUMER**, December 1994 at 3.

populations. Other drugs, however, may have population-specific ADRs. In an effort to conserve resources, the FDA's discretion to place restrictions on prescription drugs would include requiring specified tests only for identified at-risk populations. For example, in 1982 isotretinoin (Accutane) was approved for the treatment of cystic.³⁰ Since its approval, the drug has been contraindicated in women who are or may become pregnant. Despite the warnings, as of 1988 62 birth defects attributable to the drug were reported and an estimated 1000 went unreported.³¹ In addition, it is estimated that the drug has caused between 700 and 1000 spontaneous abortions and has prompted between 5000 to 7000 induced abortions.³² While the exact numbers have been disputed, the implications are clear. Women are an at-risk population who are not being protected sufficiently by educational programs and warnings of the manufacturer. One explanation for the warnings' shortfall is that not all physicians will be aware of the prescribing guidelines, and under the current regulatory scheme these physicians are not easily identified. Instead of removing Accutane from the market, the FDA could issue a regulation aimed at female patients allowing the drug to be distributed to the patient one month at a time and requiring a negative pregnancy test before each refill. These conditions would greatly reduce the risk of administering the drug to pregnant women. Prescriptions not accompanied by a pregnancy test would alert pharmacists to physicians who are not in compliance and would provide opportunities to advise non-complying physicians of the manufacturer's and the FDA's prescription guidelines.

The FDA should use these regulations to place restrictions on drugs prescribed to the largest and most vulnerable patient population: the elderly. The elderly comprise only 12 percent of the U.S. population, but consume over 33 percent of all prescription drugs.³³ In addition, studies have shown that patients over 65 suffer ADRs more frequently than young adults. Suggested reasons for their special vulnerability include changes incurred in the aging process in pharmacokinetics and pharmacodynamics, the problem of polypharmacy due to multiple pathology and problems of compliance.³⁴ Studies have estimated that the frequency of ADRs in the elderly population could be reduced by as much as 50% if physicians avoided prescribing inappropriate medication and discontinued unnecessary treatment.³⁵ To this end, regulations could be promulgated requiring periodic monitoring of elderly patients, especially those who are prescribed contraindicated drugs.

By allowing the physician to prescribe the drug in question regardless of the test results, the physician would continue to make judgement calls

³⁰Charles Marwick, *FDA Ponders Approaches to Curbing Adverse Effects of Drug Used Against Cystic Acne*, 259 JAMA 3225 (1988); see also Robert S. Stern, *V4iena Uniquely Effective Drug is Teratogenic: The Case of Isotretinoin*, 320 N. ENG. J. MED. 1007 (1989).

³¹Marwick *supra* note 30.

³²Id.

³³Richard W. Sloan, *Principles of Drug Therapy in Geriatric Patients*, 45 AM. FAM. PHYSICIAN 2709 (1992).

³⁴C.M. Lindley et al. *Inappropriate Medication is A Major Cause of Adverse Drug Reactions in Elderly Patients*. 21 AGE AND AGEING 294 (1992).

³⁵Id.

based on his own training and experience. These regulations would work to aid in the physician's judgments, ensuring that patients are monitored and that information needed for the proper balancing of risk and benefit during a certain course of treatment is gathered. Unlike regulations which would limit the prescribing of drugs to physicians with special qualifications, the proposed regulations would overcome the usual objections of the medical profession: these regulations would not substantially limit the practice of any physician and would not impose access problems for patients with a legitimate need for the medication.³⁶

Admittedly, the proposed changes to the current regulatory framework are not without costs. Foreseeable costs of these changes are the administrative costs of enacting the regulations and the costs of the required laboratory tests. It is unlikely that the administrative costs in promulgating the regulations would be any greater than those associated with removing a drug from the market altogether. The laboratory tests, in theory, were being performed by most physicians in the absence of the proposed regulations. Therefore, only those tests performed by physicians with prior poor prescribing practices are properly included in the cost of the new regulations. The benefits of the proposed regulations would be a decrease in the rates of ADRs that can be monitored through laboratory testing, which would in turn reduce health care costs. The proposed regulations also would reduce the number of highly effective drugs with serious ADRs that the FDA otherwise would have removed from the market, eliminating the costs associated with black markets and unsupervised treatment.

V. The FDA's Legal Authority to Restrict Distribution of Prescription Drugs

The FDA's authority to regulate prescription drugs is limited by the provisions of the FD&C Act. In light of these provisions and their judicial interpretation it is unlikely that the FDA currently has the authority to place the proposed restrictions on prescription drugs.

In 1972, the FDA promulgated regulations restricting the distribution of methadone to direct shipments from the manufacturer to a limited number of approved institutions. These restrictions were challenged and defeated in *American Pharmaceutical Ass'n v. Weinberger*.³⁷ The FDA reasoned that its authority under section 505(d) of the FD&C Act to refuse the approval of an NDA that is not shown to be safe included the authority to restrict the drug's distribution to reduce the likelihood of misuse.³⁸ The court found, however, that the term safe in section 505(d) meant only inherent safety of the drug when used in the manner intended, and not safety when used in other manners.³⁹ Further, the court held that any stage of the drug's genesis not specifically listed in section 505(d)(3), which deals with controls of the drug,

³⁶Robert L. Kane & Judith Garrard, *Changing Physician Prescribing Practices: Regulation & Education*, 271 JAMA 393 (1994).

³⁷377 F.Supp. 824 (D. D.C. 1974), *aff'd per curiam*, 530 F.2d 1054 (D.C. Cir. 1976).

³⁸377 F.Supp. at 828.

³⁹*Id.*

is presumably intended to be excluded from the FDA's authority.⁴⁰ Because the distribution stage is not listed, FDA does not have any authority it. The court concluded that it was the intent of Congress to confer upon the FDA the power to determine which new drugs should be permitted to enter the flow of commerce, and to confer upon all licensed practitioners the power to dispense controlled substances on an equal basis with all other approved distributors.⁴¹

On appeal, it was recognized that physicians and state-licensed pharmacists [had] not been uniformly responsible in dealing with methadone... and the FDA undoubtedly had genuine cause to believe that... effective regulation in the public interest necessitates authority on its part to restrict distribution channels.⁴² However, it was also recognized that under the current statutory framework the argument must be addressed to Congress. Because both the provisions of the FD&C Act and the concerns regarding physician irresponsibility are the same today as at the time of this judgment, it is apparent that the FDA must look to Congress to grant it authority to restrict prescription drug distribution by amending the Act.

The provisions of the FD&C Act which deal with the regulation of medical devices could serve as a model for such a Congressional amendment. Under section 520(e)(1)(B) of the FD&C Act, the FDA has the authority to require that a *medical device* be restricted upon conditions that the Secretary prescribes in a regulation, if because of its potentiality for harmful effect of its use there cannot otherwise be reasonable assurance of its safety and effectiveness. A similar provision would provide the FDA with authority to restrict the distribution of prescription drugs. For example, the Amendment might be drafted as follows:

The Secretary may by regulation require that a drug subject to section 502(b) be restricted to sale, distribution or use upon conditions as the Secretary may prescribe in such regulation if, because of identified adverse drug effects, the Secretary determines that there cannot otherwise be reasonable assurance of its safety and effectiveness. No condition prescribed under this paragraph may exclude a practitioner licensed to administer such drugs solely because the person does not have other specified qualifications.

Given the amount of resources needed to pass a Congressional amendment and given the fact that a similar amendment was proposed to Congress and never passed, the FDA should consider implementing the proposed regulations through other channels.⁴³ A non-statutory solution would be limiting reimbursement for restricted drugs under Medicare, Medicaid and private insurance systems. Reimbursement would be made for only those restricted drugs that were accompanied by the appropriate tests. Insurers, would have to bear the additional costs of the additional laboratory work. However,

⁴⁰377 F.Supp at 829.

⁴¹377 F.Supp. at 830.

⁴²American Pharmaceutical Ass'n v. Weinberger, 530 F.2d. 1054, 1056 (D.C. Cir. 1976)(per curium, McGowan concurring).

⁴³The Drug Regulation Reform Act of 1979 would have authorized the FDA to restrict the distribution of drugs. See S. Rep. No. 96-321, 96th Cong., 1st Sess. (1979).

by convincing insurers that paying for blood tests in the short term will decrease the rate of ADRs and the cost of health insurance outlays in the long run, the FDA should be able to convince the insurers to require these tests.

VI. Summary

The current framework for regulating prescription drugs does not protect patients from poor physician prescribing practices and it subjects consumers to unnecessary adverse drug reactions. An amendment to the current FD&C Act, or coordination with insurers, would enable the FDA to regulate the distribution of prescription drugs. Such regulation would reduce the rate of ADRs and provide the FDA with an alternative to removing otherwise effective drugs from the market.